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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,571	CALAS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,24,29,30,33,34,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,24,29,30,33,34,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

2. The Request for Continued Examination (RCE) filed on July 19, 2005 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

3. Claims 18-20, 24, 29, 30, 33, 34, 37 and 38 are pending.

Applicants' amendment filed March 18, 2005 is acknowledged, and applicants' response has been fully considered. Claims 18, 20, 24, 29, 30, 33, 37 and 38 have been amended, and claim 32 has been cancelled. Thus, claims 18-20, 24, 29, 30, 33, 34, 37 and 38 are examined.

Withdrawn Claim Objection

4. The previous objection to claims 18-20, 24, 29, 30, 33, 34 and 38, is withdrawn in view of applicants' amendment to the claim in the amendment filed March 18, 2005.

Withdrawn Claim Rejections - 35 USC § 112

5. The previous rejection of claim 32 under 35 U.S.C.112, first paragraph is withdrawn in view of applicants' cancellation of the claim in the amendment filed March 18, 2005.

6. The previous rejection of claims 20, 30, 33 and 38, under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, and applicants' amendment to the claim, and applicants' response at pages 9-12 of the amendment filed March 18, 2005.

Maintained Claim Objections

7. Claims 20 and 37 are objected to because of the use of "SEQ. ID NO.: 23" or "SEQ. ID NO: 23". Use of "SEQ ID NO:23" is suggested. Applicants indicate the claims have been corrected, however, these two claims are not appropriately corrected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18-20, 24, 29, 30, 33, 34, 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a linear peptide consisting of SEQ ID NO:23; a specific compound of formula (IV), $(Y)_n$-(A)-Z_m, wherein A is the amino acid sequence of SEQ ID NO:23, Z is biotin, doxorubicin or a chemical molecule of an antitumor or antibacterial agent, and wherein m=1 and n=0; or a method of vectoring the chemical molecule to a target cell *in vitro* using the conjugate of the chemical molecule with the sequence of SEQ ID NO:23, does not reasonably provide enablement for a linear peptide comprising the sequence of SEQ ID NO:23; a compound of formula (IV), wherein A is a peptide comprising SEQ ID NO:23, and Z is an active substance; a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), (A)-Z_m; or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide comprising SEQ ID NO:23. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 18-20, 24, 29, 30, 33, 34, 37 and 38 are directed to a linear peptide to vectorize active sustances, where the linear peptide comprises SEQ ID NO:23 (claims 18, 19); a compound of formula (IV) (claims 29, 30, 37 and 38); a pharmaceutical composition (claim 33) or a diagnostic agent (claim 34) comprising the compound of formula (IV); or, a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and the linear peptide comprising SEQ ID NO:23 (claims 20 and 24). The specification, however, only discloses cursory conclusions (page 8, line 19-page 13, line 7) without data supporting the findings, which state that the peptide derived from an antibiotic peptide having the formula (I) or (II), and a compound of formula (IV) containing the peptide, an active substance and a signal agent, can be used to vector one or more active substances for therapeutic and for diagnostic applications. There are no indicia that the present application enables the full scope in view of the linear peptide comprising SEQ ID NO:23; the compound of formula (IV), and the method vectoring an active substance using the linear peptide as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the linear peptides comprising the sequence of SEQ ID NO:23; the active substances and the linear peptides in the conjugates or the compounds of formula (IV), which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification only demonstrates specific analogs of protegrin and tachyplesin (e.g., SEQ ID NO:23 and other linear peptides in Tables I and II); the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines (Tables III and IV; Examples 1-4), where these in vitro results were the basis for vectoring an active substance in an organism. However, there are no working examples indicating all peptides comprising the sequence of SEQ ID NO:23 can vector different active substances into the target cells either in vitro or in vivo; or a conjugate or a compound of formula (IV) with A being a peptide comprising SEQ ID NO:23 and Z being an active substance is targeted to a specific cell or organ.

(3). The state of the prior art and relative skill of those in the art:

The related art has shown certain analogs of protegrin and tachyplesin (e.g., pages 20-22 in Lehrer *et al.* WO 96/37508), which do not have cysteines and have decreased antimicrobial activity as compared to peptides having disulfide bonds. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the vectoring effect of a peptide comprising the sequence of SEQ ID NO:23; identities of conjugates or compounds of formula (IV) of a peptide comprising SEQ

ID NO:23 and various active substances; and the effect of the conjugate in vectoring an active substance in vitro or in vivo to be considered enabling for all variants.

(4). Predictability or unpredictability of the art:

The specification indicates certain linear peptides in Table III (protegrin peptides including SEQ ID NO:23) and Table IV (tachyplesin peptides) have internalization ability toward certain cell lines (in vitro), and it appears an increase in amphipathicity have positive effect in the protegrin family, however, the specification does not provide sufficient teachings regarding internalization ability of peptides comprising SEQ ID NO:23 in the conjugate or compound of formula (IV), thus it is not readily apparent that one would have been able to predict the degree of internalization ability of a peptide comprising SEQ ID NO:23 and the vectoring effect of the conjugate containing various active substances and peptide comprising SEQ ID NO:23.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a linear peptide comprising SEQ ID NO:23, a compound of formula (IV), a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide comprising SEQ ID NO:23. The specification only discloses specific analogs of protegrin and tachyplesin (e.g., SEQ ID NO:23 and other linear peptides in Tables I and II); the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines (Tables III and IV; Examples 1-4). However, the specification has not demonstrated the

vectoring effects of various linear peptides comprising the sequence of SEQ ID NO:23, conjugates or compounds of formula (IV) containing peptides comprising SEQ ID NO:23 and various active substances. There are no working examples indicating the claimed variants and associated methods except for the conjugate of biotin-peptide or doxorubicin-peptide in vitro. Furthermore, there is no in vivo experimentation for the claimed methods. Since the specification fails to provide sufficient teachings on the vectoring effect of various peptide comprising SEQ ID NO:23 in the conjugates or compounds of formula (IV), it is necessary to have additional guidance on the identities of conjugates or compounds of formula (IV), and to carry out undue experimentation to assess the effects of the linear peptides comprising SEQ ID NO:23 in conjugates or compounds of formula (IV) for vectoring active substances to target cells, the experimentation is undue because further research is required to identify the active peptide comprising SEQ ID NO:23.

(6). Nature of the Invention

The scope of the claims includes many variants, but the specification does not provide sufficient teachings on the effect of the linear peptide comprising SEQ ID NO:23 in vectoring various active substances to target cells or organs. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants and methods, the guidance and the teaching in the specification are limited, the effect of the claimed compound is unpredictable, therefore, it is necessary to carry out undue experimentation to identify the active peptides and to assess the effects of the claimed variants in vectoring an active substance to a target cell or organ.

Response to Arguments

Applicants indicate the claims have been amended to remove the language related to "moiety of the linear peptide of sequence SEQ ID NO:23" and/or the term "peptides" as active substance; With regard to the active substances, the specification recites on pages 17-18, Example 1, a method for vectoring the following chemical molecules: biotin (fluorescent marker) and doxorubicin (anti-tumoral). Enclosed also a technical report from the inventors presenting additional working examples concerning a method for vectorizing an active substance using the peptide of sequence SEQ ID NO:23, where the active substance is: (i) a polypeptide (p. 1 - 3); (ii) an antibody (p. 5); (iii) acycloguanosine as a nucleic acid (p. 7); (iv) an oligonucleotide (p. 8); and (v) a chemical molecule (p. 10 - 17). Therefore, the claims as currently presented are enabled by the written description in the instant application (pages 7-9 of the response).

The response has been fully considered, however, the argument is not found persuasive regarding the make/use of a linear peptide comprising SEQ ID NO:23 in vectoring various active substances because the specification only shows internalization abilities of specific peptides of protegrin and tachyplesin (e.g., SEQ ID NO:23 or other linear peptides in Tables III and IV) in different cell lines (Example 3, in vitro experimentation) and the internalization of the conjugate of SM 1738 (SEQ ID NO:15) and doxorubicin (Example 4), it has not demonstrated the vectoring effects of various peptides comprising SEQ ID NO:23, or a conjugate or a compound of formula (IV) of a peptide comprising SEQ ID NO:23 in vectoring various active substances to a particular cell compartment, cell or organ, as encompassed by the claims (see above). Regarding the technical report, it only demonstrates the conjugate of an antitumor molecule such

as paclitaxel or p-doxorubicin with SEQ ID NO:23 (SynB3; pages 11-13), the conjugate of an antibacterial molecule such as vancomycin with SEQ ID NO:23 (page 16), and SynB3 enhances the cell uptake in vitro. As for the conjugate of acycloguanosine (it is not a nucleic acid) and SynB3, no cell uptake was measured (page 7). Regarding the conjugate of other active substances, it is found that either SynB1 (SEQ ID NO:25) or SynB4 (AWSFRSYRGISYRRSR, a new peptide not shown in the instant application) is used in the report, these peptides are different from the sequence of SEQ ID NO:23. Since the specification and the technical report does not provide sufficient teachings on the linear peptides comprising SEQ ID NO:23 and their effects in vectoring various active substances, it requires undue experimentation to identify the active linear peptides comprising SEQ ID NO:23, especially for in vivo effect. Thus, the specification is only enabling for a linear peptide consisting of SEQ ID NO:23, and its effect in vectoring a chemical molecule of biotin, an antitumor or antibacterial agent to a target cell *in vitro*.

9. Claims 18-20, 24, 29, 30, 33, 34, 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 18-20, 24, 29, 30, 33, 34, 37 and 38 are directed to a linear peptide comprising SEQ ID NO:23, a compound of formula (IV), a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide comprising SEQ ID NO:23. The specification discloses specific analogs of protegrin and

tachyplesin (e.g., SEQ ID NO:23 and other linear peptides in Tables I and II); the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines (Tables III and IV; Examples 1-4). However, the specification has not demonstrated the vectoring effects of various linear peptides comprising the sequence of SEQ ID NO:23, conjugates or compounds of formula (IV) containing peptides comprising SEQ ID NO:23 and various active substances. There are no working examples indicating the claimed variants and associated methods except for the conjugate of biotin-peptide or doxorubicin-peptide in vitro. Furthermore, there is no in vivo experimentation for the claimed methods. The lack of description of various linear peptides comprising the sequence of SEQ ID NO:23, and their effects of these linear peptides in vectoring various active substances for the conjugates or compounds of formula (IV) as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

10. Claims 29, 30, 33, 34, 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 29, 30, 33, 34, 37 and 38 are directed to a compound of formula (IV), (A)-Z_m, with A being a linear peptide comprising SEQ ID NO:23 and Z being an active substance; a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide comprising SEQ ID NO:23. The specification

only discloses a compound of formula (IV) is $(Y)_n$-(A)-$(Z)_m$ (page 12, line 17), it does not indicate formula (IV) is (A)-Z_m, although (A)-Z_m is a specific compound of formula (IV) when n=0. The lack of description of compounds of formula (IV) being (A)-Z_m as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 18, 19, 29, 30, 33, 34 and 37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 10-12 and 18 of co-pending application 10/270,010 based on the amended claims filed August 29, 2005; published as US 20040072340). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 18, 19, 29, 30, 33, 34 and 37 in the instant application disclose a linear peptide comprising RRLSYSRRRF (SEQ ID NO:23) and a compound of formula (IV), (A)-Zm, where A is the linear peptide, and Z is an active substance selected from the group consisting of polypeptides, antibodies, nucleic acids, oligonucleotides

and chemical molecules; a pharmaceutical composition or a diagnostic agent comprising at least one compound of formula (IV). This is obvious variation in view of claims 1, 10-12 and 18 of the co-pending application which disclose a cytotoxic T lymphocyte-inducing conjugate of an antigen coupled to a linear derivative of a protegrin (e.g., RRLSYSRRRF (SEQ ID NO:11)) or a tachyplesin lacking one or more disulfide bonds; a composition comprising the conjugate. Both sets of claims cite a conjugate of an active substance such as an antigen and a peptide sequence of RRLSYSRRRF; or a composition comprising the conjugate. Thus, claims 18, 19, 29, 30, 33, 34 and 37 in the present application and claims 1, 10-12 and 18 in the co-pending application are obvious variations of a conjugate of an active substance such as an antigen and a peptide sequence of RRLSYSRRRF; or a composition comprising the conjugate.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 18 and 19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of co-pending application 10/336312 (published as US 20030186890). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 18 and 19 in the instant application disclose a linear peptide comprising RRLSYSRRRF (SEQ ID NO:23), wherein the peptide is devoid of a disulfide bond. This is obvious variation in view of claim 5 of the co-pending application which discloses a peptide comprising a derivative of a peptide having an amino acid sequence of RRLSYSRRRF (SEQ ID NO:2) or a fragment thereof composed of a mutation such that the peptide is amphipathic. Both sets of claims cite a linear peptide comprising a sequence of RRLSYSRRRF. Thus, claims 18 and 19 in the present application and

claim 5 in the co-pending application are obvious variations of a linear peptide comprising a sequence of RRLSYSRRRF.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
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PATENT EXAMINER

CMK
September 26, 2005